REMARKS

Claims 1-27 are pending in this application and have been rejected. Applicants appreciate the Examiner's consideration of all the claims in this application.

Without acquiescing to the rejections, however, to advance prosecution, Applicants amend independent claim 1, as suggested by the Examiner, to replace "P-selectin antagonist" with "PSGL-1 protein." Applicants amend claims 2, 8 and 25, as suggested by the Examiner, to replace "P-selectin ligand activity" with "capable of treating or inhibiting thrombosis." Additionally, Applicants amend claim 23 to replace "P-selectin ligand activity" with "to treat or inhibit thrombosis." Claim 17 is amended to conform to the language of claim 1. Support for these claim amendments is found at least at, for example, page 2, lines 11-12 and lines 24-27; page 4, lines 21-29; page 10, lines 6-16; and page 31, lines 14-15. No new matter is added by these amendments. Applicants cancel claims 21 and 22 without prejudice and reserve the right to pursue these claims or claims of same or similar scope in this or a related application. Claims 1-20 and 23-27 are presented for further examination. Applicants believe that claims 1-20 and 23-27 are in condition for allowance upon the submission of this Amendment and Response, and request entry as such.

Formal Matters

Applicants have reviewed the specification for spelling errors and trademarks. Applicants have not found any trademarks or spelling errors that need to be corrected. However, should the Examiner believe that there are any trademarks or spelling errors

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that should be corrected, Applicants request that the Examiner bring them to the Applicants' attention.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1-27 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. The Examiner invited Applicants to limit the claimed "antagonists" to "PSGL-1" and the "P-selectin ligand activity" of PSGL-1 fragments to "PSGL-1" and "PSGL-1 fragments" with the activities disclosed in the specification as filed. The Examiner acknowledges that the specification is enabling for a method of using PSGL-1, including the P-selectin binding domains and fragments for the treatment of thrombosis. Office Action, at 3. However, the Examiner alleges that the specification fails to enable a method of treating thrombosis using any P-selectin antagonist or P-selectin binding (or inhibiting) fragment of PSGL. Specifically, the Examiner contends that "[t]he changes which can be made in the structure of "PSGL-1 fragments and antagonists to inhibit thrombosis" is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue." *Id.* at 4.

Applicants have amended the claims as suggested by the Examiner and respectfully request the allowance of these claims. Additionally, Applicants traverse this rejection in view of the following remarks, and respectfully submit that should the Examiner be persuaded by these remarks, Applicants would withdraw the amendments.

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The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. *United Stated v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); MPEP § 2164.01 (a). Non-critical features of the invention may be supported by a more general disclosure than those at the heart of the invention. *In re Stephens*, 180 U.S.P.Q. 659 (C.C.P.A. 1976).

The Examiner has the initial burden to show, supported by the record as a whole, why the specification is not enabling. *In re Angstadt, supra*. In the present case, the Examiner has not met this burden. Although, the Examiner may have demonstrated that some experimentation is necessary, doing so is not enough to shift the burden to Applicants to prove that such experimentation is not undue. *Id.*

In support of the enablement rejection, the Examiner cites two references: Kuntz (Science 257: 1078-1082, 1992) (hereafter "*Kuntz*"); and Ngo *et al* (The Protein Folding Problem and Tertiary Structure Prediction, 1994) (hereafter "*Ngo*"), as teaching that it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of functional P-selectin antagonists to treat thrombosis.

Applicants respectfully submit that the cited references are not pertinent to the claims in the instant application for the reasons set forth below. Applicants' claimed invention is directed to a method of treating or inhibiting thrombosis in a subject. *Kuntz* discusses an iterative approach for drug design, based on computerized modeling of

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drug-substrate complexes. Applicants submit that *Kuntz* is irrelevant to the instant claims because the claims in the instant application do not require that the P-selectin antagonist that is used for inhibition or treatment of thrombosis be a drug, or form a complex with a specific substrate. *Ngo* is largely concerned with the problem of finding an algorithm for predicting the structure of a given protein based on the amino acid sequence alone. Although, the general problem of predicting a secondary/tertiary protein structure may be of great scientific interest, Applicants submit that such prediction is not necessary to practice the invention, as recited in the claims of the instant application.

Applicants submit that although it is well known that, in some cases, even a single point mutation may result in a loss of function, it is far more likely statistically, and is commonly observed that a function is retained even when a number of amino acids have been deleted or otherwise mutated. The present specification illustrates this point perfectly. For example, even when 47 amino acids are deleted from the native PSGL-1 protein (as in dimPSGL-1), the truncated protein still retains high affinity for P-selectin and also inhibits formation of thrombi in an animal model. *See* Example 2. Similarly, the specification teaches mutated forms of PSGL-1 that may be produced, for example, by altering amino acids in the PSGL-1 protein which can reasonably be expected to inhibit or treat thrombosis and can be made using techniques conventional in the art. *See* specification at page 9, lines 1-3.

Even if a nonfunctional variant exists, it does not necessarily render a claim nonenabled. *Atlas Powder Co. v. E.I. duPont de Nemous & Co.*, 750 F.2d 1569, 1577,

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224 U.S.P.Q. 409, 414 (Fed. Cir. 1984); MPEP § 2164.08 (b). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Id.* The specification provides screening assays and animal models, that can be used for testing P-selectin antagonists for their ability to treat or inhibit thrombosis. For example, on page 43, lines 15-27, Applicants teach cell-free assays that can be used for identifying compounds that inhibit thrombosis, and further on page 45, lines 19-24 and in Example 2, Applicants provide animal models that can be used for testing the P-selectin antagonists of the invention for inhibiting thrombosis. Considering the teachings of Applicants' specification and the level of skill and knowledge in the art, one skilled in the art would be able to make and use P-selectin antagonists in the claimed methods within their full scope, without undue experimentation.

In conclusion, one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. Applicants respectfully submit that the Examiner has not met the burden of establishing that undue experimentation is required. Accordingly, Applicants request the Examiner to reconsider and withdraw the enablement rejection, in view of either Applicants' arguments or the amended claims.

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Claim Rejections under 35 U.S.C. § 102(e)

The Examiner rejected claims 1-4, 8-13, 16-18 and 20-27 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,464,778 to Cummings *et al.* (hereafter "*Cummings*"). Specifically, the Examiner alleges that "[T]he claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g., inhibiting when the thrombus inducing agent is LTC_4) would have been inherent properties of the referenced methods of treating various acute and chronic conditions associated with thrombosis . . . at the time the invention was made." Office Action, at 5.

Applicants traverse this rejection. A proper rejection under 35 U.S.C. § 102 requires that each and every limitation of the claimed invention be taught by a prior art reference. Applicants respectfully submit that *Cummings* fails to disclose each and every limitation of the claimed invention, as recited in amended independent claims 1, 23 and 25.

As discussed above, Applicants' claimed invention is directed to a method of treating or inhibiting thrombosis in a subject by administering a composition comprising an effective amount of a PSGL-1 protein to the subject, as recited in amended claim 1.

Cummings describes a glycoprotein ligand for P-selectin. *Cummings* further mentions P-selectin as having several functions relating to leukocyte adherence, inflammation, tumor metastases, and coagulation, and speculates on the use of a P-selectin ligand to modulate these conditions. *See* column 18, lines 34-39. *Cummings* fails specifically to comment on the role of P-selectin or a PSGL-1 protein in thrombosis,

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i.e., formation and development of a thrombus within a blood vessel. Whereas, *Cummings* discusses the use of a glycoprotein ligand, in particular carbohydrate moieties of such ligands, for inhibiting leukocyte adhesion and further states that inhibition of leukocyte adhesion may be desirable for reducing inflammation (*see* column 18, lines 48-50), there is no teaching in *Cummings* of such a glycoprotein or a carbohydrate moiety of a glycoprotein being useful for the treatment or inhibition of thrombosis. Additionally, *Cummings* does not disclose movement of cells relative to blood vessels or suggest that such movement would be increased by administration of a PSGL-1 protein, as recited in amended claim 23. Further, *Cummings* also does not provide any teaching of a thrombus-inducing agent including LTC_4, or that thrombus formation induced by a thrombus-inducing agent would be inhibited by administration of a PSGL-1 protein, as recited in amended claim 25.

The Examiner is contending that a treatment that may work for inhibition of leukocyte adherence and inflammation, inherently will also work for the treatment of thrombosis. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957; MPEP § 2112. In fact, Applicants provide evidence that teaches, on the contrary, that a specific composition that inhibits thrombosis, does not inhibit the alleged associated conditions of thrombosis, inflammation and leukocyte adherence. A study published by Eppihimer and Schaub (*Arterioscler. Thromb. Vasc. Biol.*, 20 (11): 2483-2488 (2000)), shows that while treatment with a recombinant form of PSGL (rPSGL-Ig) led to inhibition of

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thrombosis in animals, it had no effect on leukocyte adhesion. Specifically, *Eppihimer et al.* state at 2487:

> These results agree favourably with the present study, in which early leukocyte adhesion and transmigration were not reduced with treatment of rPSGL-Ig, but thrombosis was inhibited.

Additionally, *Eppihimer et al.* show that while treatment of animals with rPSGL-Ig led to a reduction in thrombus formation, it had no effect on inflammation. *Id.* at 2486. Applicants enclose a courtesy copy of this reference, which was previously cited in an Information Disclosure Statement dated February 26, 2003. Applicants submit that *Eppihimer et al.* was published after the priority document supporting this application.

A claim is anticipated only when each and every limitation of the claim is disclosed in a prior art reference. Without teaching treatment or inhibition of thrombosis, *Cummings* does not contain all limitations of independent claims 1, 23 and 25 and dependent claims 2-4, 8-13, 16-18, 24, 26 and 27, and accordingly, does not explicitly or inherently anticipate the claimed invention. In view of the foregoing, Applicants request that this rejection be withdrawn and believe that claims 1-20 and 23-27 are in condition for allowance.

Claims 1-5, 7-18 and 21-27 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,840,679 to Larsen *et al* (hereafter "*Larsen*"). As in case of *Cummings,* the Examiner is again alleging that "[T]he claimed structural limitations (SEQ ID NO: 2 and P-selectin binding domains thereof) and the claimed functional limitations (e.g. inhibiting wherein the thrombus inducing agent is LTC_4) would

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have been inherent properties of the referenced methods of treating various conditions associated with thrombosis with PSGL and fragments thereof . . . at the time the invention was made." Office Action, at 6.

Applicants traverse this rejection. For a prior art reference to anticipate a claim, each and every limitation of the claimed invention must be disclosed in the prior art reference. Applicants respectfully submit that *Larsen* fails to disclose each and every limitation of Applicants' claimed invention, as recited in amended claims 1, 23 and 25.

As discussed above, Applicants' claimed invention is directed to treating or inhibiting thrombosis in a subject by administering a PSGL-1 protein to the subject.

The Examiner contends that *Larsen* teaches the use of PSGL including fragments, and fragments fused to carrier molecules such as immunoglobulins, to treat conditions characterized by P-selectin mediated intercellular adhesion. Applicants respectfully submit that *Larsen* speculates on the use of an "isolated" P-selectin ligand protein in treating conditions characterized by P-selectin mediated intercellular adhesion including myocardial infarction, bacterial or viral infection, metastatic conditions etc. (*see* column 15, lines 50-66). Applicants submit that *Larsen* fails to teach a method of treating or inhibiting thrombosis using PSGL-1, or teach that thrombosis is mediated specifically by P-selectin.

The Examiner is alleging that treatment of thrombosis using a PSGL-1 protein would have been inherent in the treatment of conditions recited in *Larsen*. An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by "probabilities or possibilities." *Scaltech, Inc. v. Retec/Tetra, LLC.*, 178

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F.3d 1378, 1384, 51 U.S.P.Q.2d 1055, 1059 (Fed. Cir. 1999). As discussed above, *Eppihimer et al.*, have shown that a PSGL composition that inhibits thrombosis does not necessarily inhibit allegedly associated conditions, i.e., leukocyte adhesion and inflammation. *Eppihimer et al.* at 2486 and 2487. Additionally, Applicants respectfully submit that while *Larsen* teaches combination of P-selectin ligand protein with other factors, including thrombolytic or anti-thrombotic factors (*see* column 16, lines 27-29), *Larsen* does not teach treatment or inhibition of thrombosis by administering a composition comprising a PSGL-1 protein. In fact, these statements in *Larsen* are teaching away from the invention by suggesting that different agents should be administered to treat thrombosis.

Additionally, *Larsen* fails to disclose movement of cells relative to blood vessels or that such movement would be increased by administration of a PSGL-1 protein. *Larsen* also does not teach a thrombus-inducing agent or inhibition of thrombus formation induced by a thrombus-inducing agent by administration of a PSGL-1 protein.

In view of the foregoing, Applicants submit that *Larsen* does not teach each and every limitation of the claimed invention, explicitly or inherently, and therefore, does not anticipate independent claims 1, 23 and 25 or the associated dependent claims 2-5, 7-18, 24, 26 and 27. Accordingly, Applicants respectfully request that this rejection be withdrawn and believe that claims 1-20 and 23-27 are in condition for allowance.

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Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cummings* and *Larsen* and in further evidence of Maugeri et al., Thrombosis and Haemostasis 72: 450-456 (1994) (hereafter "*Maugeri*"). The Examiner alleges that, "[G]iven the teachings of *Cummings* and *Larsen* to inhibit PSGL-1-mediated interactions and inflammatory responses, including those associated with coronary/thrombotic conditions, the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit thrombosis, to increase the movement of cells relative to blood vessels and to inhibit the effect of thrombus-inducing agents . . . ." Office Action, at 8. Applicants respectfully submit that the Examiner did not elaborate on the inclusion of *Maugeri* in this rejection.

Applicants traverse this rejection. Applicants respectfully submit that in order to make a *prima facie* case of obviousness, the Examiner must first show that each and every limitation of the claimed invention is disclosed in the cited prior art references. Additionally, the motivation to combine the prior art references should be in the references themselves. Furthermore, even if the references could be combined, there should be a reasonable expectation of success in producing the claimed invention. MPEP § 2143. Applicants respectfully submit that the Examiner has not met the burden of making a *prima facie* case of obviousness in view of the arguments set forth below.

Applicants' claimed invention is directed to a method of treating or inhibiting thrombosis in a subject by administering a PSGL-1 protein or fragment thereof.

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As discussed above, *Cummings* discusses the role of P-selectin in leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis and further suggests that a P-selectin ligand may be used for modulating these responses. However, *Cummings* fails to disclose the role of P-selectin or PSGL in thrombosis or the treatment or inhibition of thrombosis by administering a PSGL-1 protein to a subject. *Cummings* also does not teach increasing the movement of cells relative to blood vessels or increase in such movement by administration of a PSGL-1 protein, as recited in amended claim 23. Additionally, *Cummings* fails to disclose a thrombus-inducing agent or administration of a PSGL-1 protein to inhibit thrombus formation induced by a thrombus-inducing agent, as recited in amended claim 25.

The Examiner appears to contend that a treatment used for allegedly associated conditions, leukocyte adhesion and inflammation, will also work for treatment or inhibition of thrombosis *per se*. Specifically, according to the Examiner, the claimed functional limitations would be expected properties of the referenced methods of treating artherosclerosis with PSGL and fragments thereof. Applicants respectfully submit that *Cummings* discloses artherosclerosis as being one of the pathological situations in which leukocytes can cause tissue damage (*see* column 18, line 57-32), *Cummings*, however, fails specifically to teach that PSGL or a fragment thereof, can be used for treating artherosclerosis, as contended by the Office Action. Furthermore, even if *Cummings* had explicitly taught that a PSGL-1 protein can be used for the treatment of artherosclerosis, an ordinary artisan could not have drawn an inference

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that such a treatment would also work for thrombosis. As discussed above, *Eppihimer et al.* have shown that a composition that inhibits thrombosis fails to inhibit allegedly associated conditions, for example, cellular adhesion and inflammation.

Larsen fails to cure the deficiencies of *Cummings*. *Larsen* teaches the use of isolated PSGL in the treatment of various diseases mediated by P-selectin intercellular adhesion, however, *Larsen* also fails to teach treatment or inhibition of thrombosis using a PSGL protein. Additionally, *Larsen* fails to teach movement of cells relative to blood vessels or a thrombus-inducing agent. Although, *Larsen* provides a general disclosure of combination of PSGL with other pharmaceutical compositions, including thrombolytic and anti-thrombotic agents, it does not teach treating thrombosis with a composition comprising PSGL, as discussed above. It in fact teaches the opposite, i.e., additional agents should be used for treating thrombotic diseases. In further contrast, *Larsen* provides a list of conditions mediated by P-selectin intercellular adhesion that may be treated using PSGL including myocardial infarction, metastatic conditions, inflammatory disorders and the like. Therefore, *Cummings* and *Larsen*, either alone or in combination, fail specifically to teach or suggest that thrombosis may be treated or inhibited in a subject by administration of a PSGL-1 protein to the subject, as recited in amended claim 1. They further fail to suggest that movement of cells relative to blood vessels would be increased or thrombus formation would be inhibited by administration of a PSGL-1 protein, as recited in amended claims 23 and 25, respectively. Additionally, in view of the teachings of *Eppihimer et al.*, an ordinary artisan could not have reasonably expected that a composition that may work for treating or inhibiting

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leukocyte adhesion or inflammation will also work for treatment or inhibition of thrombosis.

While the Examiner has not specifically characterized *Maugeri* in this rejection, Applicants believe that *Maugeri* is not pertinent to the instant claims. *Maugeri* discusses the role of P-selectin in the synthesis of LTC_4. Specifically, *Maugeri* teaches that an antibody against P-selectin inhibited leukocyte-platelet interaction and reduced the synthesis of LTC_4. However, *Maugeri* does not teach that LTC_4 is a thrombus-inducing agent. Applicants submit that even if *Maugeri* had characterized LTC_4 as a thrombus-inducing agent, there is no teaching in *Maugeri* of a PSGL-1 protein, or the use of such a protein for treatment or inhibition of thrombosis, for increasing movement of cells relative to blood vessels or for inhibiting thrombus formation induced by a thrombus-inducing agent. Therefore, *Maugeri* fails to cure the deficiencies of *Cummings* and *Larsen*.

In view of the foregoing, Applicants respectfully submit that none of *Cummings, Larsen*, or *Maugeri,* alone or in combination, teach each and every limitation of the claimed invention, as recited in amended claims 1, 23, and 25, or the associated dependent claims 2-20, 24, 26 and 27. Accordingly, Applicants request that this rejection be reconsidered and withdrawn.

Claims 25-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cummings* and *Larsen* as applied to claims 1-27 above and in further evidence of *Maugeri* and Johnston *et al.* (J. Immunol. 159:4514-4523, 1997) (hereafter "*Johnston*").

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The Examiner is alleging that, "[O]ne of ordinary skill in the art would have expected that the methods of treating thrombotic conditions taught by *Cummings* and *Larsen* would have inhibited the thrombus inducing agent in a subject, including LTC_4 at the time the invention was made. Further both *Maugeri* and *Johnston* teach that inhibiting P-selectin-mediated events results in the inhibition of thrombus-inducing biological substances, including LTC_4." The Examiner is further alleging that "[G]iven the teachings of *Cummings* and *Larsen* to inhibit PSGL-1-mediated interactions and inflammatory responses . . . the ordinary artisan would have had a reasonable expectation of success at the time the invention was made to treat or inhibit and to inhibit the effect of thrombus-inducing agents . . . ." Office Action, at 9.

Applicants traverse this rejection. As discussed above, in order to make a *prima facie* case of obviousness, the Examiner must first show that each and every limitation of the claimed invention is disclosed in the cited prior art references. Additionally, the motivation to combine the prior art references should be in the references themselves. Furthermore, even if the references could be combined, there should be a reasonable expectation of success in producing the claimed invention. MPEP § 2143. Applicants respectfully submit that the Examiner has not met the burden of making a *prima facie* case of obviousness in view of the arguments set forth below.

Applicants claimed invention, as recited in amended claim 25, is directed to a method for inhibiting thrombus formation induced by a thrombus-inducing agent in a subject by administering an effective amount of a soluble PSGL-1 protein or fragment.

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Applicants submit that none of *Cummings*, *Larsen*, *Maugeri or Johnston*, alone or in combination, teach each and every limitation of the claimed invention.

As discussed above, *Cummings* discusses the role of P-selectin in leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis and further suggests that a P-selectin ligand may be used for modulating these responses. However, *Cummings* fails to disclose the role of P-selectin or PSGL in thrombosis or the treatment or inhibition of thrombosis by administering a PSGL-1 protein to a subject. Additionally, *Cummings* also fails to disclose a thrombus-inducing agent, or that thrombus formation induced by such an agent would be inhibited by administration of a PSGL-1 protein.

Also, as discussed above, *Larsen* teaches the use of isolated PSGL in the treatment of various diseases mediated by P-selectin intercellular adhesion, however, *Larsen* fails to teach treatment or inhibition of thrombosis using a PSGL protein. Additionally, also as acknowledged by the Examiner, *Larsen* fails to disclose a thrombus-inducing agent or that thrombus formation induced by a thrombus-inducing agent would be inhibited by administration of a PSGL protein.

While *Maugeri* discloses LTC_4 and further teaches that a P-selectin antibody can inhibit the synthesis of LTC_4, it fails specifically to disclose a soluble PSGL-1 protein. Whereas *Maugeri* posits that polymorphonuclear leukocyes and platelets cooperate in processing arachidonic acid-derived intermediate metabolites into biologically active substances that play a pathophysiological role in inflammation and thrombosis, and further that LTC_4 may be produced in this system (*See Maugeri* at 450), *Maugeri* does

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not explicitly teach that LTC_4 is a thrombus-inducing agent. Applicants submit that even if *Maugeri* had explicitly characterized LTC_4 as a thrombus-inducing agent, there is no teaching or suggestion in *Maugeri* that thrombus formation induced by LTC_4 would be inhibited by administration of a PSGL-1 protein.

Therefore, none of *Cummings*, *Larsen* or *Maugeri*, alone or in combination, teach or suggest inhibiting thrombus formation induced by a thrombus-inducing agent in a subject by administration of a PSGL-1 protein.

Johnston does not cure the deficiencies of *Cummings*, *Larsen* and *Maugeri*, alone or in combination. Specifically, *Johnston* teaches that in case of LTC_4-induced acute inflammation, there is an increase in leukocyte rolling flux, a decrease in leukocyte rolling velocity, and an increase in leukocyte adhesion. *Johnston*, further teaches that the increase in leukocyte rolling flux, decrease in leukocyte rolling velocity, and increase in leukocyte adhesion were reversed by a P-selectin antibody. However, *Johnston* fails to disclose a PSGL-1 protein and also does not teach or suggest that LTC_4 is a thrombus-inducing agent. Further, even if *Johnston* had taught that LTC_4 is a thrombus-inducing agent, there is no teaching or suggestion in *Johnston* that a composition that may inhibit conditions associated with LTC_4 induced inflammation will have any effect on thrombosis or thrombus-formation induced by LTC_4. In fact, Applicants' argument is further substantiated by *Eppihimer et al.* who have shown that a specific composition that inhibits thrombosis does not necessarily inhibit the alleged thrombosis associated conditions, cellular adhesion and inflammation. Therefore, one of ordinary skill in the art could not reasonably have drawn an inference based on

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Johnston that an agent that induces inflammation would also induce thrombosis, or a composition that reverses a condition associated with LTC_4 induced inflammation would have any effect on LTC_4 induced thrombosis.

Therefore, none of *Cummings*, *Larsen*, *Maugeri* or *Johnston* teach or suggest a method of inhibiting thrombus formation induced by a thrombus-inducing agent by administering a PSGL-1 protein.

In view of the foregoing, Applicants request that this rejection be withdrawn and submit that claims 25-27 are in condition for allowance.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that claims are fully enabled by the specification, and are unobvious in view of the prior art references. Applicants therefore respectfully request the reconsideration and withdrawal of the rejections and the timely allowance of the pending claims. Should the Examiner not believe that the claims are in condition for allowance, Applicants request that she please contact their undersigned representative at (202) 408-4086 for an interview to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

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Respectfully submitted,

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Dated: May 28, 2003

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APPENDIX TO THE AMENDMENT

MARKED-UP VERSION OF AMENDMENTS TO THE CLAIMS

1. (Amended) A method of treating or inhibiting thrombosis in a subject comprising administering a composition comprising an effective amount of a PSGL-1 protein to the subject [P-selectin antagonist].

2. (Amended) The method of claim 1, wherein the PSGL-1 protein [P-selectin antagonist] is a soluble PSGL-1 protein or a fragment thereof, capable of treating or inhibiting thrombosis [having P-selectin ligand activity].

8. (Amended) The method of claim 2, wherein the soluble PSGL-1 protein comprises an extracellular domain of human PSGL-1 protein[,] or a fragment thereof, capable of treating or inhibiting thrombosis [having P-selectin ligand activity].

17. (Amended) The method of claim 1, wherein the PSGL-1 protein [P-selectin antagonist] is administered to the subject prior to thrombus formation.

23. (Amended) A method for increasing the movement of cells relative to blood vessels in a subject comprising administering a composition comprising an effective amount of soluble PSGL-1 protein or a fragment thereof, and allowing the PSGL-1 protein or fragment thereof to treat or inhibit thrombosis, thereby increasing the movement of cells relative to blood vessels [having P-selectin ligand activity].

25. (Amended) A method for inhibiting thrombus formation [the effect of a] induced by a thrombus-inducing agent in a subject comprising administering a composition comprising an effective amount of [an effective amount of] soluble PSGL-1

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protein[,] or a fragment thereof, wherein the PSGL-1 protein or fragment is capable of treating or inhibiting thrombosis [having P-selectin ligand activity].

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